REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claims 23, 28, 29, 45, 47, 48, and 54 have been amended to further clarify the invention. After entry of the present Amendment, claims 20 to 54 will be pending.

Applicants submit the claim amendments are supported throughout the specification, including at lines 26-35 on page 10 and Example 6 beginning on page 46, and present no issues of new matter.

Formal Matters

The Examiner objected to the abstract. Applicants have amended the abstract as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

The Examiner objected to the copy quality of Figure 15A. A new version of Figure 15A has been submitted for the Examiner's consideration. Withdrawal of the objection is respectfully requested.

The Examiner objected to the form of claim 54 under 37 CFR 1.75(c). Claim 54 has been amended to proper dependent form. Withdrawal of the objection is respectfully requested.

The Examiner objected to claims 28, 29 and 48 because of informalities in the claims. Applicants have amended the claims as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

Indefiniteness

The Examiner rejected claims 20-54 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection.

The Examiner maintains it is essential that human VEGF be specified in the claims. Applicants disagree. Applicants specifically define the terms "VEGF" and "native VEGF" in the specification. See, for example, the specification beginning at page 10, line 34:

> The terms "VEGF" and "native VEGF" as used herein refer to the 165-amino acid vascular endothelial cell growth factor and related 121-, 189-, and 206- amino acid vascular endothelial cell growth factors, as

> described by Leung et al., *Science*, 246:1306 (1989) and Houck et al., *Mol. Endocrin.*, 5:1806 (1991), (and further provided in Figure 1A and 1B), together with the naturally occurring allelic and processed forms thereof. The terms "VEGF" and "native VEGF" are also used to refer to truncated forms of the polypeptide comprising amino acids 8 to 109 or 1 to 109 of the 165-amino acid vascular endothelial cell growth factor.

Applicants submit the definition of the terms meets Applicants' burden of reasonable particularity and distinctness and serves the notice function required by § 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent. MPEP § 2173.02. Therefore, it is not necessary to specify "human VEGF" in the claims.

The Examiner maintains all claims with the limitation "wherein the amino acid substitutions increase the relative binding affinity ratio of KDR to FLT-1" are indefinite. Applicants have directed the claims to VEGF variants with the claimed amino acid substitutions "wherein the VEGF variant polypeptide has selective binding affinity for KDR receptor as compared to native VEGF." The term "selective" is defined in the specification. See, for example, the specification at page 10 beginning at line 26:

> When binding affinity of such VEGF variant to the KDR receptor is approximately equal (unchanged) or greater than (increased) as compared to native VEGF, and the binding affinity of the VEGF variant to the FLT-1 receptor is less than or nearly eliminated as compared to native VEGF, the binding affinity of the VEGF variant, for purposes herein, is considered "selective" for the KDR receptor.

Applicants submit the amended claims comply with the definiteness requirement of § 112, second paragraph.

The Examiner maintains claims 45 and 46 are incomplete as they fail to adequately identify the cells to be used. Applicants have amended the claims as suggested by the Examiner.

The Examiner maintains claim 54 depends from a cancelled claim. Applicants have amended the claim to depend from claim 50.

Based on the forgoing, Applicants submit the claims comply with the requirements of 35 U.S.C. § 112, second paragraph. Withdrawal of the rejection is respectfully requested.

Anticipation/Obviousness

The Examiner rejected claims 23, 32, 36-44, 46, 47, and 53 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Fuh et al., 1998, *JBC*, 273:11197-11204. Applicants respectfully traverse this rejection.

To anticipate a claim, each and every element of the claim must be described, either expressly or inherently, in a single prior art reference. Verdegaal Bros. v. Union Oil of California, 814 F.2d 628, 631 (Fed. Cir. 1987). Fuh et al. teach a VEGF variant comprising amino acid substitutions at residues 17 and 64. Unlike the claimed VEGF variants, the variants disclosed by Fuh et al. do not have selective binding affinity for KDR receptor as compared to native VEGF. The binding affinity of the Fuh variants for KDR monomer is 2 fold less than native VEGF. The binding affinity of the Fuh variants for KDR dimer is 200 fold less than native VEGF. See text at p. 11202, 1st paragraph, and Table II. Therefore, Fuh et al. do not disclose all of the elements of Applicants' claims.

Fuh et al. do not anticipate the claimed VEGF variants. The cited reference does not disclose all the elements of Applicants' claim. Therefore, withdrawal of the anticipation rejection is respectfully requested

The Examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. MPEP § 2142. Three criteria must be met by the Examiner to establish a prima facie case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). The Examiner has failed to establish one or more of the three criteria.

As discussed above, the variants disclosed by Fuh et al. do not have selective binding affinity for KDR receptor as compared to native VEGF. The binding affinity of the Fuh variants for KDR monomer is 2 fold less than native VEGF. The binding affinity of the Fuh variants for KDR dimer is 200 fold less than native VEGF. Therefore, Fuh et al. do not teach or suggest all of the limitations of Applicants' claims.

Fuh et al. teach away from the claimed VEGF variants. Fuh et al. teach that substitution of amino acids 17 and 64 reduces the binding affinity of VEGF for KDR receptor. Consequently, one of skill in the art would not have been motivated to substitute a) one or more amino acids at residues 63 to 66 of native VEGF and one or more amino acids at residues 17 to 25 of native VEGF or b) one or more amino acids at residues 17 to 25 of native VEGF to generate VEGF variants that have selective binding affinity for KDR receptor as compared to native VEGF. Nor would one of skill in the art have had a reasonable expectation of successfully generating a VEGF variant that had selective binding affinity for KDR receptor as compared to native VEGF.

Based on the forgoing, Applicants submit the Examiner has failed to establish a *prima facie* case of obviousness. The Examiner has not met any of the three required criteria. Accordingly, withdrawal of the obviousness rejection is respectfully requested.

Conclusion

In light of the foregoing Amendment and Remarks, Applicants' assert the claims are in condition for allowance. Early notice of allowable claims is requested.

The Examiner is invited to telephone the undersigned attorney for clarification of any of these Remarks or Amendments, or to otherwise speed prosecution of this case.

Respectfully submitted,

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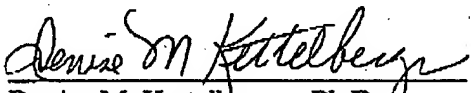
Date: 20 November 2003



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